43. (once amended) The process according to claim 40, wherein the crystallization from a water-miscible organic solvent comprises dissolving the HMG-CoA reductase inhibitor in acetone, and then adding water thereto.

44. (twice amended) The process according to claim 40, wherein said crystallization from an organic solvent having limited miscibility with water comprises dissolving the HMG-CoA reductase inhibitor in said organic solvent at a concentration of 10 to 35 g/L, and removing one-third to three-fourth of said organic solvent.

45. (twice amended) The process according to claim 40, wherein ethyl acetate is used as the organic solvent having limited miscibility with water.

## REMARKS

The Examiner has requested a new substitute specification, although a substitute specification was submitted with Response A, filed January 24, 2002. Applicant is confused by the repeated requests for substitute specifications. Nonetheless, for the convenience of the Examiner, yet another substitute specification is being supplied with this Response B, in the form of the published PCT application, plus the substitute sheets filed during the International Stage. Applicant kindly requests that the Examiner call if this substitute specification is not satisfactory so that this matter may be expedited without additional delay.

Claims Rejections - 35 USC § 112, para. 2 - Indefiniteness

The Examiner rejected Claim 40 under paragraph 2 of §112 as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." See p. 2 of Office Action dated April 23, 2002.

Claim 40 is amended to delete the phrase "wherein the limited solubility is in the range of about 0.25 g/100 mL and about 30 g/ 100 mL." This phrase was inadvertently and erroneously introduced into claim 40 in the previously-filed Response A, as can be seen from a comparison of claim 40, as written in Version with Markings to Show Changes, versus claim 40 without markings (see Response A). The Version with Markings does not include this phrase; as such, it has been deleted in the version of claim 40 (twice-amended) filed with this Response B. The undersigned apologizes for this error and the resulting confusion. In addition, a list of applicable limited miscibility solvents, as disclosed in the application on p. 7, lines 26-36, is added to twice-amended claim 40.

Claims Rejections - 35 USC § 112, para. 1

Claims 24-47 are rejected as containing new matter which was not described in the specification. Specifically, the Office Action asserts that deletion of the term "limited-miscibility" leaving just "organic solvent" impermissibly "broadens the phrase to include such solvents such as ethanol, methanol, acetone, etc." See Office Action, p.2. The Office Action also asserts that the temperature range limitation for dissolving the inhibitor in an organic solvent is likewise deemed new matter without support in the specification (*see Id.*, p. 3).

In order to remove the basis for the latter assertion, Claim 24 is amended to delete the phrase relating to dissolving the inhibitor before crystallization at a temperature range of between about 10 to 40 °C, and the phrase "having limited miscibility with water" is inserted to describe the second organic solvent.

In order to address the former assertion, as suggested by the Examiner, claim 24 (and claim 40) is further amended to include a listing of applicable limited miscibility organic solvents, as disclosed on p. 7, lines 26-36 of the application. Applicant respectfully submits that the 35 U.S.C. § 112, para. 1 rejection has been addressed and thus, claim 24 is in condition for allowance.

In like manner, claims 36-37 and claim 44 are amended to include the phrase "having limited miscibility with water." These amendments are made so that all claims depending from claims 24 and 40 use the same language as stated in amended claims 24 and 40 of Response A (i.e. "limited miscibility with water" only, not "limited miscibility or solubility with water"), thereby making all independent and dependent claims consistent in this regard. Applicant respectfully submits that the original "limited miscibility or solubility with water" phrase is redundant, and that by removing the words "or solubility" from the phrase, the claims more clearly set forth the invention. Support for these amendments is found in the application, p. 9, lines 1-8.

Finally, claims 34-35 and 42 are hereby amended to describe a "water-miscible" organic solvent instead of a "water miscible or water-soluble" organic solvent. As with amended claims 36-37 and claim 44 (see above), these amendments make the claims consistent with claims 24 and 40, previously amended in like manner in Response A, from which claims 34-35 and claim 42 depend, respectively.

In light of the above amendments, it is respectfully submitted that the bases for the §112, para. 1 and 2 rejections have been removed. Applicant respectfully submits that all claims are thus in condition for allowance.

Claim Rejections - 35 USC § 102 (b)

Claims 40-42 and 46 remain rejected under 35 USC § 102(b) as being "clearly anticipated by US 4,319,039 [AB]." (See p.3, second paragraph.)

Applicant has amended claim 40 as suggested by the Examiner, replacing the open-ended phrase "comprise" with the close-ended phrase "consist of" in line 3 of claim 40.

In addition, Applicant re-emphasizes that the presently claimed invention, with two combined crystallization steps, one involving the use of a water-miscible solvent and the other the use of an organic solvent having limited miscibility with water, is not anticipated by US 4,319,039, Albers-Schonberg et al. The Office Action states that the '039 patent discloses crystallization of the inhibitor from first "a mixture of chloroform/methanol/$NH_4OH$/ether (water immiscible) .... followed by crystallization from ethanol." See Office Action, p. 4. However, the '039 patent's protocol has two alternative pathways for purification of the HMG-CoA reductase inhibitors. The first involves recrystallization of the crude ammonium salt from the chloroform mixture (limited miscibility solvent) (see col. 13, lines 22-28) followed by a final purification from hot isopropanol with 5% concentrated ammonium hydroxide (a second limited miscibility solvent) (see col. 13, lines 61-68).

The alternative purification pathway involves converting the crude ammonium salt to the lactone form using toluene under reflux conditions, (limited miscibility

solvent) (see col. 13, lines 29-37), recystallizing the lactone from ethanol (water miscible solvent) (see col. 13, lines 43-45) and then converting the lactone back to the ammonium salt by 1) dissolving the lactone in basic methanol and filtering; 2) evaporating the methanol; 3) redissolving in acidic ethyl acetate; and 4) precipitating with a mixture of chloroform/methanol/concentrated $NH_4OH$ followed with acetone (second limited miscibility solvent) (see col. 13, lines 46-59). The resulting crude ammonium salt product is subjected to final purification by crystallization from hot isopropanol with 5% concentrated ammonium hydroxide (third limited miscibility solvent) (see col. 13, lines 61-68).

Thus, the '039 patent does not disclose combined crystallization steps consisting of only two crystallization steps wherein one involves an organic solvent with limited miscibility with water and the other involves a water-miscible organic solvent, as required by amended claims 40-46 in the present application.

In addition, the presently claimed invention results in HMG-CoA reductase inhibitors with greater than 99.6 % purity while maintaining high overall yields (see examples 1, 2, 4 and 5). In contrast, the '039 patent discloses a purification scheme that results in greater than or equal to 99 % purity for the lactone (see col. 13, lines 43-45) which is further purified to the ammonium salt form at greater than or equal to 99.5 % purity (see col. 14, lines 1-4). However, there are no results, in fact, evidencing successful purification as high as 99.6 % purity or greater, with concomitant high yields.

Applicant respectfully submits that such high purity, while maintaining high yields, is very difficult to achieve, because of undesired side products having similar structures to the desired inhibitor co-purifying with the desired inhibitor. Therefore,

conventional purification schemes such as disclosed in the '039 patent may lead to high purity, but at purities greater than 99.6 % (if attained at all by such methods) the loss in yield is significant.

In summary, Applicant respectfully submits that the '039 patent does not anticipate the presently claimed invention as amended.

## CONCLUSION

Claim 47 has been cancelled, and claims 24, 34-37, 40, and 42- 45 have been amended to eliminate the indefinite terms and the new matter. Specifically, in claim 40, the term "organic solvent" has been replaced with the term "organic solvent having limited miscibility with water," and applicable solvents have been included as a list in the claims, for which there is support in the specifications on p. 7, lines 26-36. In addition, the phrase "wherein the limited solubility is in the range of about 0.25 g/ 100 mL and about 30 g/ 100 mL," has been deleted because it was inadvertently and erroneously added in Response A. Therefore, Applicant respectfully submits that claim 40 no longer contains new matter, and is no longer indefinite.

Also, Applicant respectfully submits that claim 40, as amended to clarify the scope of the combined crystallization steps, is not anticipated by the '039 patent.

For the reasons set forth above, it is submitted that all pending claims are in condition for allowance. Reconsideration of the claims and a notice of allowance are therefore requested.

Applicant hereby petitions for a one-month extension of time, and includes a check for $110 for the extension fee. It is believed that only a one-month extension of

time is needed; however, this conditional petition for an extension of time is being made in the event that the need for a further extension has been overlooked. If any additional fees are required for the timely consideration of this application, please charge deposit account number 19-4972. The Examiner is requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

Date: August 15, 2002

Respectfully submitted,

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Version with Markings to Show Changes

24. (twice amended) A process for the isolation and purification of HMG-CoA reductase inhibitors from mycelium biomass which comprises:

clarifying a mycelium broth and concentrating the clarified broth to a lower volume,

acidifying [~~of~~] the concentrate to a pH value in the range of 4.5 to 7.5, followed by extracting the HMG-CoA reductase inhibitor with ethyl acetate;

optionally performing lactonization;

crystallizing the HMG-CoA reductase inhibitor from:

i) a water miscible organic solvent; and

ii) an organic solvent having limited miscibility with water including higher alkyl alcohols such as butanol, isobutanol, amyl alcohol, hexanol, 2-ethylhexanol, benzyl alcohol and cyclohexanol, higher alkyl ketones such as methylbutyl ketone, methyl isobutyl ketone and cyclohexanone, esters such as methyl acetate, ethyl acetate, n-propyl and isopropyl acetate, t-butyl, isobutyl and sec-butyl acetate and amyl acetate, ethers such as diethyl ether and diisopropyl ether, chlorinated hydrocarbons such as methylene chloride and chloroform, acetonitrile and the like, including mixtures of these solvents [~~wherein before crystallization, the inhibitor is dissolved in said organic solvents at a temperature of between about 10 to 40°C~~].

34. (once amended) The process according to claim 24, wherein the water-miscible [~~or water soluble~~] organic solvent used in the crystallization step is acetone or a low alkyl alcohol.

35. (once amended) The process according to claim 24, wherein the crystallization step from a water-miscible [~~or water-soluble~~] organic solvent comprises dissolving the HMG-CoA reductase inhibitor in acetone, and then adding water thereto.

36. (twice amended) The process according to claim 24, wherein the crystallization step from an organic solvent <u>having limited miscibility with water</u> comprises dissolving the HMG-CoA reductase inhibitor in said organic solvent at a concentration of 10 to 35 g/L, and removing one-third to three-fourth of said organic solvent.

37. (twice amended) The process according to claim 24, wherein the organic solvent <u>having limited miscibility with water</u> used in the crystallization step is ethyl acetate.

40. (twice amended) A process for the purification of HMG-CoA reductase inhibitors which comprises subjecting the HMG-CoA reductase inhibitor to combined crystallization steps, which [~~comprise~~] <u>consist of</u> crystallization from a water-miscible organic solvent and crystallization from an organic solvent <u>having limited miscibility with water including higher alkyl alcohols such as butanol, isobutanol, amyl alcohol, hexanol, 2-ethylhexanol, benzyl alcohol and cyclohexanol, higher alkyl ketones such as methylbutyl ketone, methyl isobutyl ketone and cyclohexanone, esters such as methyl acetate, ethyl acetate, n-propyl and isopropyl acetate, t-butyl, isobutyl and sec-butyl acetate and amyl acetate, ethers such as diethyl ether and diisopropyl ether, chlorinated hydrocarbons such as methylene chloride and chloroform, acetonitrile and the like,</u>

including mixtures of these solvents, [~~wherein the limited solubility is in the range of about 0.25 g/100 mL and about 30 g/100 mL,~~] as final steps to obtain HMG-CoA reductase inhibitors having a purity higher than 99.6%.

42. (once amended) The process according to claim 40, wherein acetone or a low alkyl alcohol is used as the water-miscible [~~or water soluble~~] organic solvent.

43. (once amended) The process according to claim 40, wherein the crystallization from a water-miscible [~~or water soluble~~] organic solvent comprises dissolving the HMG-CoA reductase inhibitor in acetone, and then adding water thereto.

44. (twice amended) The process according to claim 40, wherein said crystallization from an organic solvent having limited miscibility with water comprises dissolving the HMG-CoA reductase inhibitor in said organic solvent at a concentration of 10 to 35 g/L, and removing one-third to three-fourth of said organic solvent.

45. (twice amended) The process according to claim 40, wherein ethyl acetate is used as the organic solvent having limited miscibility with water.